As the profession of neurology becomes increasingly subspecialized, it becomes more and more difficult for general neurologists to feel comfortable with every category of disease. At no time is this felt more keenly than when an imaging procedure has been performed on a patient for a seizure, headache, or focal neurologic complaint and a brain tumor is discovered. In contrast to consulting with a patient with a movement disorder or neuromuscular disease, there is no time to craft the discussion and discuss a differential diagnosis. As with demyelinating disease or stroke, the scan result dictates an immediate conversation with the patient, but in contrast to those disorders this takes place from the perspective of a provider who understands that the eventual outcome for the patient is likely to be guarded. How to give that message with tact, candor, and some optimism could be the sole topic of this article but, instead, we focus on 5 new ideas that are changing the management of brain tumor patients in the hopes that these points might prove useful during those times.

**PROGNOSIS AND GLIOMA SUBTYPES**

In his pioneering work “Death Foretold,” Dr. Nicholas Christakis\(^1\) says “prognosis gives diagnosis its affective component, striking fear in patients and physicians alike.” There has traditionally been a lot of therapeutic nihilism about the treatment of glioblastoma, but that is now changing. Previously believed to be one homogeneous group of tumors based on clinicopathologic and histologic assessments, we are now finding that subgroups exist within these tumors that one day may allow us to better predict which chemotherapy option is best for each individual patient. In addition, this begins to explain how some of our patients with glioblastoma multiforme have lived 10 years when others die of their disease in 2–3 months. The cell of origin of the glioblastoma has never been defined but there is a theory\(^2\) that neural stem cells, astrocytes, oligodendrocytes, and other cell types undergo mutation and become a brain cancer–propagating cell which then develops various genetic changes to become 4 separate glioblastoma subtypes: classic, mesenchymal, neural, and proneural. A fifth type of glioblastoma is termed a “secondary glioblastoma” and arises out of a lower grade I/II astrocytoma by de-differentiation over time. The classic glioblastoma demonstrates gains on chromosome 7 and losses on chromosome 10 with amplification of epidermal growth factor receptor and no alterations in TP53; this subtype is therefore responsive to chemoradiotherapy. The mesenchymal type overexpresses angiogenic markers making them a likely target for drugs such as bevacizumab, which inhibits vascular endothelial growth factor. The proneural type is more often seen in younger patients and is associated with improved survival and, finally, the neural type has the genetic signature most like normal brain. Knowledge of the genetic changes in these tumors may someday lead to more targeted therapies, improved quality of life, and prolonged survival.

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Some of this promise has already been realized for the less than 5% of gliomas that are oligodendrogliomas. Combined loss of chromosomes 1P and 19Q within the tumor has become a powerful predictor of both chemotherapy response and survival as independent entities. This is so reliable, and standard histology so fraught with error, that the 1p-19q deletion has become a diagnostic marker for oligodendrogliomas and is being used by some pathologists to change their ultimate histologic read. Ensuring that a newly diagnosed patient with a suspected high-grade glioma understands that the disease is more complex than here-tofore thought and has the opportunity to discuss new advances in surgery, chemotherapy, and radiation therapy with a multidisciplinary team is more important now than it has ever been in the past.

**DIAGNOSIS AND IMAGING MIMICS** It is very important to remain aware of the clinical and radiographic mimics of brain tumor as well of those times when patients who harbor brain tumors have clinical presentations that mimic other diseases. Acute stroke in the luxury perfusion stage is probably the most common mimic of a brain tumor. More importantly, of course, a brain tumor patient who has had several seizures can often be quite clinically similar to a patient who has had a subacute stroke, though diffusion MRI sequences are making differentiating between those 2 possibilities somewhat less of a problem. Perfusion CT scan can also be quite helpful in differentiating stroke from tumor by showing hypoperfusion as would be expected, rather than hyperperfusion seen in tumors. It is known that tumefactive MS needs to be considered in the differential diagnosis of a brain tumor but less well known is that, radiographically, demyelinating disease can also mimic a high-grade butterfly glioma (figure 1). This case report was of a 58-year-old woman who presented with personality change and was found to have a contrast-enhancing lesion, which crossed the corpus callosum and lacked the usual partial ring enhancement often seen in cases of MS. On the more esoteric end of the spectrum, in children, mitochondrial disorders can mimic brainstem tectal gliomas (figure 2). This report was of a group of 3 children who all shared the clinical features of various types of visual disturbance and high T2 signal in the periaqueductal gray matter that suggested a tectal glioma on MRI scan; all of these children proved to have a mitochondrial ND5 subunit mutation.

![Figure 1 MRI of demyelinating disease mimicking tumor](image-url)
Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, has been used increasingly as salvage therapy for glioblastoma and now also for initial therapy in clinical trials. Because our traditional radiographic response criteria (Macdonald) were based on the degree of contrast enhancement of the tumor bed, and because bevacizumab has such a profound effect on capillary leakage, our ability to correctly interpret MRI scans is compromised. Edema, mass effect, and contrast enhancement may respond dramatically to treatment with this drug but a slow increase in fluid-attenuated inversion recovery (FLAIR) signal abnormality may suggest that the tumor has changed to a more infiltrating lower grade tumor type. To try to understand these changes better, we are beginning to use other MRI modalities such as diffusion to help interpret the changes. Because tightly packed tumor cells can create changes in brain water, there have been pathologically confirmed cases showing that diffusion MRI can detect tumor progression which otherwise might be misdiagnosed as a treatment-related stroke.7

**TREATMENT AND PSEUDOPROGRESSION**

Temozolomide is an oral drug, which is rapidly absorbed and changed into MTIC (methyltriazeno-imidazole-carboxamide), a DNA-methylating drug. MGMT (methyl-guanine methyltransferase), a DNA repair enzyme, can overcome this attack by removing the methyl group but it then gets destroyed in the process; cells that lack MGMT have been shown to have increased sensitivity to temozolomide.8 The European Organisation for Research and Treatment of Cancer study on the concomitant use of radiation therapy and adjuvant temozolomide in glioblastoma patients showed a median survival of 14.6 months compared with radiation therapy alone (12.1 months). Additional molecular analysis showed that 2-year survival for those patients whose tumors had methylated MGMT gene promoters was 46%, whereas those with unmethylated promoters had only a 2-year survival rate of 14%.

Paradoxically, as we have more treatment successes, the rate of early MRI change suggesting tumor progression has increased to 21% within the first 2 months of treatment. Increase in contrast enhancement and mass effect can mimic tumor progression. The term “pseudoprogression” is now being used to describe what is likely a significant inflammatory reaction to effective treatment. Increasing steroid doses can control the edema and continuation of chemotherapy should be considered in all of those patients whose MRI scans seem to “progress” during the first 3 months of chemotherapy, particularly if they remain clinically unchanged.

Figure 2 MRI showing a periaqueductal high T2 signal on axial T2 (A) and sagittal T2 (B) and an enlargement of the tectum that mimicked tectal glioma in all 3 children (case 1, 9 years; case 2, 6 years; case 3, 7 years)
TREATMENT AND ANTIPILEPTIC DRUGS

Prophylactic use of antiepileptic drugs (AEDs) is not recommended in patients with brain tumor due to lack of efficacy. With the increasing use of more chemotherapeutic drugs in patients with brain tumors, the interactions between AEDs and chemotherapy have come under greater scrutiny. Corticosteroid activity can be altered unpredictably, cleared faster and with a shorter half-life in patients receiving phenobarbital or phenytoin. In addition, since many chemotherapy drugs are cleared through the cytochrome P450 system in the liver, the induction of these enzymes can cause diminished efficacy of the chemotherapy drug or breakthrough seizures. Because of the complexity of most drug regimens and the availability of IV levetiracetam, initiating anticonvulsant therapy with this drug alone, or changing patients to this drug early after their initial brain surgery, is becoming standard of care.9 Interestingly, it has also recently been reported that levetiracetam can actually inhibit MGMT and sensitize cells to temozolomide, another reason to make this drug first-line monotherapy.10

There has traditionally been a lot of therapeutic nihilism about the treatment of glioblastoma, but that is now changing

PROGNOSIS AND QUALITY OF LIFE ISSUES

Perhaps the most important role that we can play in the lives of our brain tumor patients and their families is to know as much as we can about how to improve quality of life (QOL) rather than focus solely on increased survival. In the early years, there was no QOL component to brain tumor clinical trials and it is only recently that QOL questionnaires have become part of the data collection. A recent review of this topic in the brain tumor population found, not surprisingly, that the complexity of disability is quite high.11 The incidence of common symptoms reported was fatigue (90%–94%), sleep disturbance (32%–52%), headache (50%), and cognitive impairment (50%). Studies of mood showed that the incidence of depression (7%–90%) and anxiety (30%–60%) was reported more variably. Interestingly, because the incidence of seizures is higher in low-grade glioma patients than in high-grade glioma, the presence of seizures was a positive prognostic factor when other symptoms were not present. Early use of neurocognitive evaluation and treatment is, therefore, quite important. Ritalin, modafinil, and Aricept have all been shown to have a positive effect on mood and cognition.

Despite our best efforts, though prognosis is clearly improving, there remains no cure for high-grade glioma. Helping patients achieve a peaceful death is just as much a part of our job as helping them survive longer. There is a lot of caregiver and patient anxiety about how brain tumor patients die and we desperately need more knowledge about this phase of the end of life. An Italian study of 169 brain tumor (primary and malignant) patients who died at home13 and a study from the Netherlands involving 55 HGG patients13 found very similar results regarding the incidence of key symptoms in the last weeks of life. Seizures occurred in nearly half of the patients, especially in the last week of life. Dysphagia (85%), headache (36%), agitation and delirium (15%), and death rattle (12%) were most common. Dysphagia is a particularly complex symptom, described usually as present 70%–80% of the time. Some studies, however, report it occurring only 10%–15% of the time and the discrepancy appears to relate to loss of consciousness (LOC). When LOC is excluded, true dysphagia only occurs 14% of the time. Body pain occurs much less frequently (25%) in the brain tumor population than in patients with systemic cancer (60%–80%) and families find this information reassuring. Most patients (82%) showed progressive loss of consciousness leading to deep coma in the last week of life and this was felt by the families to represent a peaceful death. Seizures and death rattle were most upsetting, but seizures could be controlled with rectal valproate, rectal diazepam, or subcutaneous midazolam and rattle secretions with slight dehydration and anticholinergic drugs. Steroid doses were progressively reduced (45%) after patients lost consciousness, leaving a small dose to avoid adrenal failure. Cause of death was presumed brain herniation 73% of the time, the remainder due to pulmonary embolism, infection, bowel perforation from steroid use, and following seizures. In the Netherlands study,13 66% died at home, 17% died in the hospital, and 8.5% each for hospice and nursing home. There is a pressing need for better designed, prospective QOL studies of brain tumor patients and their caregivers; currently our European colleagues appear to be leading the way.

Familiarity with emerging knowledge about brain tumor subtypes, caution about interpretation of MRI, understanding of the importance of changing anticonvulsant treatment, and early education of patients and their families about symptom management combined with the best decision about surgery, radiation therapy, and chemotherapy will allow us to take better care of our brain tumor patients in the future.
DISCLOSURE
Dr. Taylor serves on the editorial advisory board for Neurology Now.

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